The sialy-glycolipid SSEA4 marks a subpopulation of chemotherapy resistant breast cancer cells with mesenchymal features

We identified the sialy-glycolipid SSEA4 as a constant marker of chemotherapy-resistant cancer cells in all four models. In addition, SSEA4 expression was found higher in 3 out of 4 TNBC PDx that are de novo resistant to neo-adjuvant chemotherapy compared to sensitive TNBC PDx. Two cell populations with different percentage of SSEA4- positive (SSEA4+) and with different growth characteristics were identified in a PDx model. When treated with genotoxic compounds, the cell population with higher SSEA4+ expression showed increased resistance to chemotherapy, indicating this post-translational modification as potential marker of tumor resistance. Comparison of SSEA4+ and SSEA4-negative (SSEA4-) tumor cells from TNBC PDx models by global gene expression profiling showed overexpression of mesenchymal-associated genes in SSEA4+ tumor cells and a deregulation of drug resistance pathway-associated genes and miRNAs. In addition, high expression of ST3 beta-galactoside alpha-2,3-sialyltransferase 2 (ST3GAL2), the enzyme catalysing the last step of SSEA4 synthesis, was found associated with poor outcome in breast and ovarian cancer patients treated with chemotherapy.

We propose SSEA4 as a novel marker of epithelial-mesenchymal transition associated with chemoresistance, and ST3GAL2 expression as a predictive marker for tumor chemoresistance associated with poor outcome in breast and ovarian cancer patients. Both biomarkers and additionally identified regulatory miRNAs may be used to further understand chemoresistance and to develop alternative treatment regimens for breast and ovarian cancer patients.